

APPENDIX B

AGENTS, SUBSTANCES, MIXTURES, OR EXPOSURE CIRCUMSTANCES DELISTED FROM REPORT ON CARCINOGENS

The agents, substances, mixtures or exposure circumstances contained in this appendix had been previously listed in the Report on Carcinogens as either *known or reasonably anticipated to be human carcinogens*. Those substances removed from the Report prior to the 1996 establishment of a formal review procedure for delisting listings from the Report are contained in the following table with the reason for delisting. The reason for delisting is, for some, a lack of exposure to residents of the United States to these chemicals/ substances (since they are no longer produced or used), or for others, because there has been a revision in the rulings/findings as to the carcinogenic potential of these entries (due to new studies, etc.). The last Report on Carcinogens in which these chemicals/ substances appeared, and to which reference can be made for all information available, is also given in this table.

Those previously listed substances that have been delisted from the Report as a result of a formal review for delisting (Eighth Edition forward) are also contained in this table. A profile for those substances delisted from the Report as a result of a formal review for delisting is included in this appendix. These profiles summarize the reviews for delisting and include the relevant information and the issues identified by the scientific review groups that led to the substance s delisting from the Report on Carcinogens. Background documents outlining in more detail the issues considered during the reviews for delisting these substances can be obtained by contacting the National Toxicology Program at the following address: National Toxicology Program, Report on Carcinogens, P.O. Box 12233, MD EC-14, Research Triangle Park, NC 27709.

Substance Name	CAS Number	Last Listing	Reason for Delisting
Chloramphenicol	56-75-7	<i>known carcinogen</i> First Report (1980)	Human data considered inadequate
Aramite	140-57-8	<i>reasonably anticipated carcinogen</i> Fourth Report (1985)	No U.S. residents exposed
N,N-bis(2-Chloroethyl)-2-naphthylamine (Chlornaphazine)	494-03-1	<i>known carcinogen</i> Fourth Report (1985)	No U.S. residents exposed
Cycasin	14901-08-7	<i>reasonably anticipated carcinogen</i> Fourth Report (1985)	No U.S. residents exposed
Methyl iodide	78-88-4	<i>reasonably anticipated carcinogen</i> Fourth Report (1985)	Re-evaluated by IARC; now considered "equivocal"
5-Nitro- <i>o</i> -anisidine	99-59-2	<i>reasonably anticipated carcinogen</i> Fifth Report (1989)	Insufficient evidence of carcinogenicity
<i>p</i> -Nitrosodiphenylamine	156-10-5	<i>reasonably anticipated carcinogen</i> Fifth Report (1989)	Insufficient evidence of carcinogenicity
Ethyl acrylate	140-88-5	<i>reasonably anticipated carcinogen</i> Eighth Report (1998)	See following profile
Saccharin	81-07-2	<i>reasonably anticipated carcinogen</i> Eighth Report (1998)	See following profile

Summary
Report on Carcinogens Review Group¹ Actions on the Nomination of Ethyl Acrylate for Delisting from the Report on Carcinogens

Ethyl Acrylate
CAS No. 140-88-5

Ethyl acrylate is used in various industries as an intermediate in the production of emulsion-based polymers which are then used in paint formulations, industrial coatings, and latex products. It is also used as a synthetic flavoring substance and fragrance adjuvant in consumer products. Human exposure to ethyl acrylate occurs mostly through inhalation of ethyl acrylate vapors, but it may also result from skin contact or ingestion as a food additive or by drinking contaminated water. The Report on Carcinogens review groups considered the data underlying the nomination to remove ethyl acrylate from the Report on Carcinogens where it has been listed as *reasonably anticipated to be a human carcinogen* since 1989. The basis for this listing was a gavage study which resulted in dose-related benign and malignant forestomach neoplasms in rats and mice. The Basic Acrylic Monomer Manufacturers, Inc. (BAMM), submitted a nomination to remove ethyl acrylate from the Report on Carcinogens based upon the following: 1) negative tumorigenicity results from chronic studies using routes other than gavage in corn oil; 2) research results suggesting that the forestomach carcinogenicity observed in the gavage studies was secondary to a site-specific and concentration-dependent irritating effect of ethyl acrylate; and 3) that significant chronic human oral exposure to ethyl acrylate monomer is unlikely in light of current manufacturing practices and patterns of usage (see summary of ethyl acrylate carcinogenicity data below).

The majority opinion of the Report on Carcinogens review groups was to recommend that ethyl acrylate be removed from the Report on Carcinogens. This was based on the facts that 1) the forestomach tumors induced in animal studies were seen only when ethyl acrylate was administered by gavage at high concentrations that induced marked local irritation and cellular proliferation, 2) animal studies by other routes of administration including inhalation were negative, and 3) because significant chronic human oral exposure to high concentrations of ethyl acrylate monomer is unlikely. Therefore ethyl acrylate does not meet the criteria to be listed in the Report on Carcinogens as reasonably anticipated to be a human carcinogen.

Summary of Available Carcinogenicity Data and Other Relevant Information²
Animal Studies

Although mutagenic in some *in vitro* tests, ethyl acrylate is not genotoxic under *in vivo* physiological conditions perhaps due to its rapid metabolism to acrylic acid and ethanol by carboxyesterases and detoxification through binding to non-protein sulfhydryls. Target tissue toxicity comprised of irritation has been observed in the skin in a lifetime mouse skin painting study, in the nasal olfactory mucosa in 27-month inhalation studies in rats and mice, and in the forestomach in two-year corn oil gavage studies in rats and mice. Only body weight reduction was observed in a two-year dosed-water study in rats. The forestomach carcinogenicity observed in the corn oil gavage studies represents the only treatment-related tumorigenic response in the various animal studies. The irritation, hyperplasia, and tumor responses in the forestomach were related more to target tissue concentration of ethyl acrylate than to delivered dose in the chronic gavage study. Based upon stop-exposure studies, gavage doses of ethyl acrylate in corn oil

sufficient to induce sustained mucosal hyperplasia in the forestomach must be administered for longer than six months to induce forestomach neoplasia.

Human Exposure and Cancer Studies

Prolonged consumer exposure to high levels of ethyl acrylate monomer by the oral route is unlikely. Potential significant exposures would most likely occur in an occupational setting where the routes of exposure would be dermal and/or inhalation. Ethyl acrylate has a strong acrid odor (odor threshold ~ 0.5 ppb) and is a known irritant to the skin, eyes, and mucous membranes, making it unlikely that humans would be chronically exposed to high concentrations. Data provided in the BAMM nomination on worker exposure show occupational exposure well below the threshold limit value (TLV=5 ppm for an eight-hour time-weighted average) and the short-term exposure limit (STEL=15 ppm), although exposure of painters in an unventilated room has been reported as high as 8 ppm in the painter's breathing zone.

An epidemiology study reported on mortality from cancer of the colon and rectum in three separate cohorts of workers from two plants manufacturing and polymerizing acrylate monomers. Workers were exposed to ethyl acrylate and methyl methacrylate monomer between 1933 and 1982. Risks for both types of cancer were associated with exposure in the earliest cohort, although the rectal cancer results are imprecise because of the small number of cases involved. The greatest relative risk was found in workers with the highest level of exposure and a 20 year latency. The other two cohorts, with later dates of hire, showed no excess risk, but very few cases were available for observation. This study, by itself, can neither establish nor rule out a causal relationship of ethyl acrylate with cancer.

ACTION ON NOMINATION

Ethyl acrylate will be delisted from the Report on Carcinogens because the relevant data are not sufficient to meet the current criteria to list this chemical as *reasonably anticipated to be a human carcinogen*. This is based on the fact that the forestomach tumors induced in animal studies were seen only when the chemical was administered by gavage at high concentrations of ethyl acrylate, that induced marked local irritation and cellular proliferation, and because significant chronic human exposure to high concentrations of ethyl acrylate monomer is unlikely.

¹ Review groups for the Report on Carcinogens include the following:

The NIEHS Review Committee for the Report on Carcinogens (RG1)

The NTP Executive Committee* Interagency Working Group for the Report on Carcinogens (RG2)

*Agencies represented on the NTP Executive Committee include: Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Center for Toxicological Research (NCTR), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA), Department of Health and Human Services (DHHS), National Institutes of Health (NIH), National Cancer Institute (NCI), and National Institute of Environmental Health Sciences/NTP (NIEHS/NTP)

The NTP Board of Scientific Counselors Report on Carcinogens Subcommittee (the External Peer Review Group)

² Summary of data contained in December, 1998 Ethyl Acrylate Background Document

Summary

Report on Carcinogens Review Group Actions on the Nomination of Saccharin for Delisting from the Report on Carcinogens

Saccharin **CAS No. 81-07-2**

Saccharin and its sodium and potassium salts have been produced commercially in the United States for over 80 years. It is primarily used as a nonnutritive sweetening agent. Potential exposure to saccharin occurs through the consumption of dietetic foods and drinks and by use of some personal hygiene products. Potential exposure to saccharin also occurs in the workplace, specifically in occupations, industries, or facilities that produce and deal with saccharin and its salts. The Report on Carcinogens review groups considered the data underlying the nomination to remove saccharin from the Report on Carcinogens where it has been listed as *reasonably anticipated to be a human carcinogen* since 1981. The basis for this listing was sufficient evidence of carcinogenicity in experimental animals. The Calorie Control Council submitted a nomination to the NTP to consider removing saccharin from the Report on Carcinogens based upon mechanistic data related to development of urinary bladder cancers in rats (see summary of saccharin carcinogenicity data below).

The majority opinion of the review groups was to recommend that saccharin be delisted from the Report on Carcinogens. There is evidence for the carcinogenicity of saccharin in rats but less convincing evidence in mice. Studies indicate that the observed urinary bladder cancers in rats are related to the physiology of the rat urinary system including urinary pH, osmolality, volume, and the presence of precipitate, and urothelial damage with attendant hyperplasia following consumption of diets containing sodium saccharin at concentrations of 3% or higher with inconsistent findings at lower dietary concentrations. The factors thought to contribute to tumor induction by sodium saccharin in rats would not be expected to occur in humans. The mouse data are inconsistent and require verification by additional studies. Results of several epidemiology studies indicate no clear association between saccharin consumption and urinary bladder cancer. Although it is impossible to absolutely conclude that it poses no threat to human health, sodium saccharin is not reasonably anticipated to be a human carcinogen under conditions of general usage as an artificial sweetener.

Summary of Available Carcinogenicity Data and Other Relevant Information¹

Animal Studies

In four studies of up to 30 months duration, sodium saccharin was carcinogenic in Charles River CD and Sprague-Dawley male rats as evidenced by a dose-related increased incidence of benign or malignant urinary bladder neoplasms at dietary concentrations greater than 1% (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980, Schoenig *et al.* 1985). Non statistically significant increases in urinary bladder cancer have also been seen in saccharin treated female rats from studies showing a positive effect in males (Arnold *et al.* 1980, Taylor *et al.* 1980). Furthermore, several initiation/promotion studies in different rat strains have shown a reduced latency and/or increased incidence of similar urinary bladder cancers in male and female rats fed sodium saccharin subsequent to treatment with different urinary bladder initiators (e.g.,

Hicks and Chowanec 1977, Cohen *et al.* 1979, Nakanishi *et al.* 1980a, West *et al.* 1986, Fukushima *et al.* 1990). Several additional rat studies in which sodium saccharin was administered either in the diet or in drinking water were negative for tumorigenicity (Fitzhugh *et al.* 1951, Lessel 1971, Schmh 1973, Chowanec and Hicks 1979, Hooson *et al.* 1980, Schmh and Habs 1984).

Three mouse studies have reported positive carcinogenicity following exposure to saccharin. Two of these studies involved surgical implantation of saccharin-containing cholesterol pellets into the urinary bladders and resulted in development of malignant urothelial neoplasms (Allen *et al.* 1957, Bryan *et al.* 1970). In the third study, dietary sodium saccharin resulted in increased incidences of malignant thyroid neoplasms (Prasad and Rai 1986). While the mouse data cannot be discounted, some of these studies had methodological flaws, provided limited information, did not show a dose-response, or had unexpected outcomes that may be species or strain-specific and should be verified by additional studies. Four studies in mice were judged negative for tumorigenesis (Roe *et al.* 1970, Kroes *et al.* 1977, Homberger 1978, Frederick *et al.* 1989) as were limited studies in nonhuman primates (McChesney *et al.* 1977 abstr., Sieber and Adamson 1978, Thorgierson *et al.* 1994, Cohen *et al.* 1996 abstr.) and a single hamster study (Althoff *et al.* 1975).

Human Cancer Studies

Most of the relevant human epidemiology studies have examined associations between urinary bladder cancer and artificial sweeteners, rather than saccharin per se. The time trend data for bladder cancer show no clear indication that the increased use of saccharin or artificial sweeteners commencing in the 1940s is associated with a general increase in bladder cancer when controlled for confounding factors, chiefly smoking. Risks of bladder cancer in diabetics, who presumably consume greater amounts of artificial sweeteners compared to the general population, are not greater than risks in the general population (Armstrong and Doll 1975). Based upon several case-control studies there is no overall association of use of artificial sweeteners and bladder cancer (reviewed by IARC 1980, 1987b, JEFCA 1993). However, an association between use of artificial sweeteners and bladder cancer cannot be ruled out in some case-control subgroups, albeit involving small numbers (Howe *et al.* 1980, Hoover and Strasser 1980, Cartwright *et al.* 1981, Morrison *et al.* 1982, Mommsen *et al.* 1983). Taken together, while the available epidemiology data show no consistent evidence that saccharin is associated with increased bladder cancer in general, a small increased risk in some subgroups, such as heavy users of artificial sweeteners, cannot be unequivocally excluded. With regard to the general population, if sodium saccharin is a risk factor, it is weak and cannot be proven or disproved due to lack of actual exposure data and intrinsic limitations of existing epidemiology studies.

Additional Information Relevant to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Extensive studies of the mutagenicity and genotoxicity of saccharin have shown generally negative but occasionally conflicting results. Sodium saccharin is essentially nonmutagenic in conventional bacterial systems (reviewed by Ashby 1985, IARC 1987a,b, Whysner and Williams 1996) but is weakly clastogenic or genotoxic in short-term *in vitro* and in some *in vivo* test systems (reviewed by Ashby 1985, IARC 1987a,b, Whysner and Williams 1996). Urine from mice treated with sodium saccharin was mutagenic in the Ames test in one study (Batzinger *et al.*

1977). Saccharin does not covalently bind to DNA and does not induce unscheduled DNA synthesis in bladder urothelium.

Saccharin-induced carcinogenesis in rats shows a sex predilection for males (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980), an organ specificity for urinary bladder (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980, Fukushima *et al.* 1983, Schoenig *et al.* 1985), and a dose-response when exposure to dietary concentrations of 1 to 7.5% of the sodium salt of saccharin was begun early in life (beginning at birth or immediately at weaning) and continued for approximately two years (Schoenig *et al.* 1985). The results of mechanistic studies have shown that certain physiological conditions must be simultaneously or sequentially present for induction of urinary bladder tumorigenesis. These conditions include a urinary pH greater than 6.5, increased urinary sodium concentration, increased urine volume, decreased urine osmolality, presence of urinary crystals or precipitate, with resulting damage to the urothelium prompting a proliferative (hyperplastic) response of the urinary bladder epithelium. All of these conditions have been studied extensively in male rats but less so in females or in mice. The high levels of urinary protein characteristically produced by male rats may partially explain the sex predilection. The high intrinsic rate of urothelial proliferation at about the time of weaning is also believed to contribute to the observed tumorigenic effects. The urinary milieu in rats, especially male rats, is sufficiently different from that in humans or other species to support the contention that these observations are rat-specific. Pharmacokinetic and metabolism data on sodium saccharin do not explain the male rat sensitivity for induction of urinary bladder neoplasms (Sweetman and Renwick 1979, 1980).

ACTION ON NOMINATION

Saccharin will be delisted from the Report on Carcinogens, because the rodent cancer data are not sufficient to meet the current criteria to list this chemical as *reasonably anticipated to be a human carcinogen*. This is based on the perception that the observed bladder tumors in rats arise by mechanisms not relevant to humans, and the lack of data in humans suggesting a carcinogenic hazard.

¹ Summary of data contained in the October, 1997, Saccharin Background Document.

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